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RESEARCH ARTICLE

Application of metal complexes of schiff base with special reference to thiosemicarbazone: a review

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ABSTRACT

Schiff bases have been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. Thiosemicarbazone derivatives are used in organic synthesis and they are used in evaluating new product that possesses different biological activities. This review covers updated information on the most active Thiosemicarbazone derivatives that have been reported to show considerable pharmacological actions such as, anticonvulsant, antidepressant and other biological activity. The Chemistry of Schiff bases is a field that is being no- ticed. Schiff base ligands are considered privileged li- gands because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines. In this review, the synthesis, biological activities along with application of Schiff base and their complexes are summarized from 1976-2013.

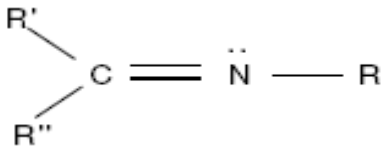
Key words: Schiff Bases; Metal Complexes; Thiosemicarbazone; Antibacterial; Biological Activities

INTRODUCTION:

Metals have played an important role in medicine for years, ever since human being started to walk on the planet. Many are essential to our diets in varying quantities, although people have only recently realized their significance. Introducing metal ions into a biological system may be carried out for therapeutic or diagnostic purposes, although these purposes overlap in many cases.

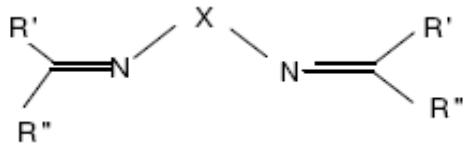
Metals not only provide templates for synthesis, but they also introduce functionalities that enhance drug delivery vectors.

Schiff bases are condensation products of primary amines with carbonyl compounds and they were first reported by Hugo Schiff in 1864. The common structural feature of these compounds is the azomethine group with a general formula RHC=N-R' where R and R' are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. These compounds are also known as anils, imines or azomethines[1].



Where R stands for a phenyl or alkyl group which makes the Schiff base a stable imine.

The bridged Schiff's bases have the following structure which contains many functional groups able to change according to the purpose required.



Where R' = H or alkyl group, R" = phenyl or substituted phenyl, X = alkyl or aryl group

A large number of Schiff bases and their complexes have been studied for their interesting and important properties, e.g., their ability to reversibly bind oxygen[1], catalytic activity in hydrogenation of olefins[2] and transfer of an amino group[3], photochromic properties[4], and complexing ability towards some toxic metals.

Although the Schiff bases are known to be good chelating agents, and easily prepared and characterized, little interest has been given to their uses for analytical purposes because of two serious drawbacks, they are insoluble in aqueous solutions and they decompose easily in acidic solutions, limiting their use to basic conditions.[5]

When two equivalents of salicylaldehyde are combined with a diamine, a particular chelating Schiff base is

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produced. The so-called Salen ligands with four coordinating sites and two axial sites open to ancillary ligands. Although the term Salen was used originally only to describe the tetradentate Schiff bases derived from ethylenediamine, the more general term Salen-type is used in literature to describe the class of [O,N,N,O] tetradentate Schiff base ligands.[6]

Metal complexes appear to provide a rich platform for the design of novel chemotherapeutic drugs. We can choose the metal itself and its oxidation state, the numbers and types of coordinated ligands and the coordination geometry of the complexes. The ligands can not only control the reactivity of the metal, but also play critical role in determining the nature of secondary coordination sphere interactions involves in the recognition of biological target sites such as DNA, enzymes and protein receptors. Also the ligands themselves can sometimes undergo biologically-important redox reactions or other modifications(e.g hydrolysis) *in vivo* mediated by the metal. These variables provide enormous potential diversity for the design of metallo-drugs.

Schiff bases, having azomethine (RHC=N-R') group and their metal complexes are widely used for industrial purposes and also reveal a wide range of biological applications.

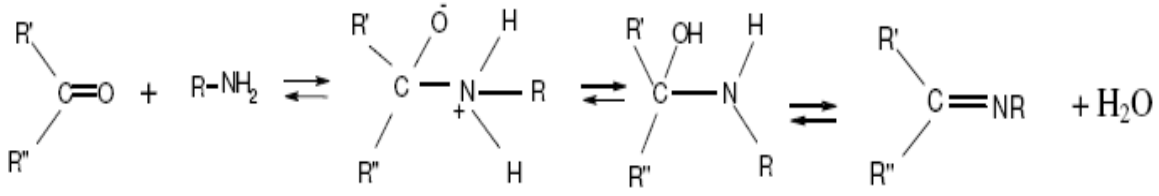
An interesting application of Schiff's bases is their use as an effective corrosion inhibitor, which is based on their ability to spontaneously form a monolayer on the surface to be protected[7].

Many metal complexes of hydroxyethylidene diphosphonic acid (HEDP), ethylenediamine methylphosphoric acid (EDMP), ethylene diamine – bis (methyl phosphoric) acid (EDBMP), ethylene diamine–N, N, N^{I}, N^{I}– tetrakis (methy phosphonic) acid (EDTMP), ethylene diamine – N, N^{I} – bis(phenyl methylene phosphonic)acid (EDPMP), ethylene–diamine–N,N^{I}–bis(O–hydroxyphenyl methylene phosphonic) acid (EDBHPMP), (EDDBMP), (DTPMP), (DTBDMP, (PMDBDMP) etc. have been reported.[8-10]

Large number of transition metal complexes have been synthesized and charatarised with schiff's bases which have been proved of wide utility, semicarbazone and thiosemicarbazone have joined special attentation due to their activity against protozoa, influenza, small pox, malaria, tuber–culosis[11-12], and antitumor activity of their meatal complexes.[13-14] Metal complexes of thiosemicarbazone have emerged as new class of chemotherapeutic agent which exhibit inhibitory activity against most cancers through inhibition of a crucial enzyme, obligatory for DNA biosynthesis and cell division. Due to wide range of medicinal use of metal complexes of semicarbazone/thiosemicarbazone. Co(II), Ni(II), Cu(II) etc. metal complexes with theses ligands have been prepared and reported.[15-16]

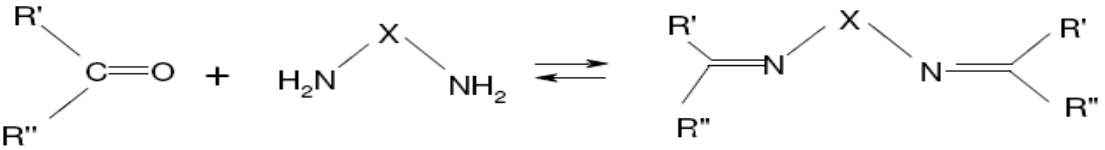
SYNTHESIS OF SCHIFF BASES:

There are several reaction pathways to synthesise Schiff bases. The most common is an acid catalysed condensation reaction of amine with an aldehyde or ketone under refluxing conditions (Scheme **-1**). The first step in this reaction is an attack of nucleophilic nitrogen atom of amine on the carbonyl carbon, resulting in a normally unstable carbinolamine intermediate. The reaction can reverse to the starting materials, or when the hydroxyl group is eliminated and a C=N bond is formed and the product is called imine. Many factors affect the condensation reaction, for example the pH of the solution as well as the steric and electronic effects of the carbonyl compound and amine. In acidic solutions the amine is protonated, thus cannot function as a nucleophile and the reaction cannot proceed. Furthermore, in very basic reaction conditions the reaction is hindered as sufficiently protons are not available to catalyse the elimination of the carbinolamine hydroxyl group. In general, aldehydes react faster than ketones in Schiff base condensation reactions as the reaction centre of aldehyde is sterically less hindered than that of ketone. Furthermore, the extra carbon of ketone donates electron density and thus makes the ketone less electrophilic compared to aldehyde.[7]



Scheme -1: Prepartion of Schiff's bases.

For preparation of the bridged Schiff's bases a diamine compound is required with two molecules of aldehyde or ketone according to the structure of the product of interest as in the following reaction.



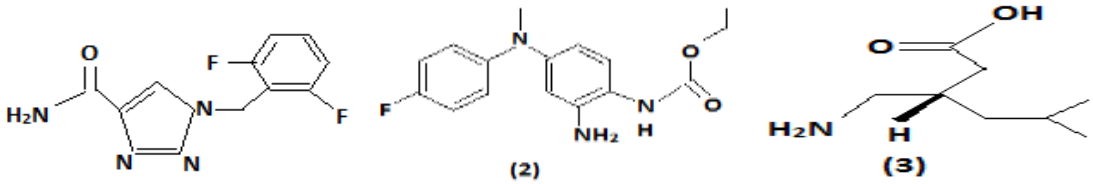
Scheme -2

Where R' = H or alkyl group
R" = phenyl or substituted phenyl
X = alkyl or aryl group

APPLICATION OF SCHIFF BASES:

In Epilepsy:

Epilepsy, one of the most frequently neurological disorder, is a major public health issue, affecting about 4% of individuals over their life time.[17] Recent studies revealed that a number of aryl semicarbazones possessed anticonvulsant activity in the maximal electroshock (MES) and subcutaneous pentylene – tetrazole (ScPTZ) screens when administered by the intraperitoneal route to mice.[17 – 23] In recent year aryl and heteroaryl semicarbazones and thiosemicarbazones have emerged as structurally novel anticonvulsants.[24] Aryl semicarbazones have also been reported to display excellent anticonverlsant activityin mice and rats[25]. During the past decades, several new drugs have been apporved like Ruffinamide (1), Retigabine(2), Pregabaline(3) etc.



(2) (3)

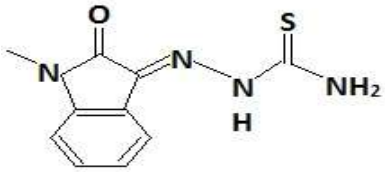
(Structures of Rufinamide, Retigabine and Pregabaline)

Despite advances in the drug treatment of epilepsy, a number of limitations of antiepileptic drug therapy continue to exit. Thus, the search for new anticonvulsant drugs continues to be active area of investigation in medicinal chemistry[19].

As Anti-Viral Agents:

Metal complexes have a higher position in medicinal chemistry. The therapeutic use of metal complexes in cancer and leukemia are reported from the sixteenth century. In 1960 an inorganic complex cisplatin was discovered, today more than 50 years, it is still one of the world's best selling anticancer drug. Metal complexes formed with other metals like copper, gold, gallium, germanium, tin, ruthenium, iridium was shown significant antitumor activity in animals. Schiff base with silver show considerable antiviral activity. Example silver complexes in oxidation state showed inhibition against cucumber mosaic virus.

In the recent studies, appear to be structural class with antipox virus activity[26]. Isatin derivatives such as methisazone (marboran(4)), the β – thiosemicarbazone of N – methyl isatin have been described as smallpox chemopropylactic agents[27].



Structure of methisazone (marboran)

Methisazones descreases morbidity and mortality in susceptible contacts but it has direct therapeutic efficiency vs variola and is no longer manufactured as a drug substances[28].

As Anti-neplastic agents:

It has been proved that thiosemcarbazone block DNA synthesis in mammalian cells big by inhibiting the enzymes, ribonucleosidediphosphate reductase, presumably either via chelation with an iron ion required by the enzymes or because a performed metal chellate of the inhibitor interacts with the target enzyme[29-31]. The reports also point out the capacity of thiosemicarbazon to saver the DNA stands[32]. A major clinical challenge in successfull treatment of cancer with anti cancer drugs is

that certain tumor cells develop a particular pheno type called multidrug resistance (MDR), which makes these cells resistant to other classes of anticancer agents to which the tumor cells have not been treated previously[33.] Synthesis and characterization of palladium complex of phenanthrene quinone thiosemicarbazone and evaluation of its anti proliferatives properties in the breast cancer cells and normal cells have been described[34]. The study suggest that the complex is a potent anti neo plastic agents that has selective activity against tumor cells and is effective against drug resistant breast cancer cells.

The mechanism of biological activity of thiosemicarbazones is due to their ability to inhibit the biosynthesis of DNA, possibly by blocking the enzyme ribonucleotide diphosphate reductase; binding to the nitrogen bases of DNA, hindering or blocking base replication; creation of lesions in DNA stands by oxidative rupture Metal-based drugs are the most widely used drug in chemotherapy. The gallium, titanium salts have been shown to have anti-cancer activity. In the mid-1960s, Bernett Rosenberg and his co-workers(1965) serendipitously discovered that cis-dichloro-diammine platium(II) (cis- [Pt(NH3)2Cl2], cisDDP, cisplatin) exhibited antitumor activity but trans isomer, trans [Pt(NH3)2Cl2], did not. Cisplatin, (cis-[PtCl2[(NH3)2] also known as cis-DDP is perhaps the best known example of a small molecule metal-containing drug.

Carboplatin entered the clinic in 1998, principally in response to the necessity to reduce the toxic side effects of the parent drug(Christian, 1992)[35]. One series of Ferrocifens was made by replacing the aromatic phenyl in the β position of tamoxifen with an aromatic ferrocenyl of slightly greater bulk and lipophilicity, ferrocifen was synthesized via Mc-Murry coupling reaction.

Anti-inflammatory agents:

Metal complexes of organic drugs have also been used as anti-inflammatory and antiarthritic agents. Extensive research is being conducted into Au, Cu and Zn anti-inflammatory drugs that have fewer side effects with similar or higher efficacy than the parent organic drugs commonly in use. Gold compounds were first used in 1929 by French doctors to treat rheumatold arthritis(Shaw, 1999)[36] and remain important in the treatment of rheumatic diseases. Several injectable transition gold complexes like sodium aurothiomalate, aurothioglucose and sodium aurothiopropanol are used clinically in the treatment of severe cases of rheumatold arthritis. (Rafique *et al*, 2010)[37]

Zhuo *et al*, (2000)[38] reported the synthesis and characterization of anti inflammatory Zn(II) and Cu(II) complexes of indomethacin. The studies were undertaken in order to reduce the side effects associated with the clinical use of indomethacin and related carboxylate–containing nonsteroidal anti-inflammatory drug (NSAID).
Investigation of anti-inflammatory activity of complexes of diclofenac was carried out by Kovala-Demertzi *et al*,2000, 2001). The Binuclear copper(II) complex of diclofenac [Cu(L)2(H2O)]2. 2H2O was found to have an anti-inflammatory profile superior to diclofenac when inhibiting inflammations due mainly to the activation of lipooxygenase and or to the complement systems. Other metal complexes of diclofenac synthesized by this group are Co(II), Ni(II) and Pd(II). These complexes exhibit a superior anti –inflammatory profile, inhibiting inflammations and phagocytosis and act as antioxidant compounds, properties that are absent in diclofenac.

As Corrosion Inhibitor:

An interesting application of Schiff bases is their use as an effective corrosion inhibitor which is based on their ability to spontaneously form a monolayer on the surface to be protected [39]. Schiff bases have been found to posses more inhibitor efficiency than their constituent carbonyls and amines [40]. Schiff bases derived from condensation reaction of cinnamaldehayde with 2-aminophenol and cinnamaldehyde with phenylene diamine studied as inhibitor for corrosion of carbon steel in acidic media 0.5 N HCl by Mohammad Qasim Mohammad. The results indicated that these Schiff bases inhibited the corrosion efficiently. Some authors have attributed these considerably stronger inhibition efficiencies to the presence of unoccupied π*- orbitals in the Schiff base molecules, which enable electron back donation from the metal d-orbitals and thereby stabilize the existing metal-inhibitor bond, which is not possible with the constituent amines [41].

Antifungal agents:

Many metal complexes have powerful antifungal activities and and are already in common day to day use such as silverderma (Silver complex of sulfadiazine) and Flammazine (Zinc complex of silverdiazine.) Navarro *et al,* (2001)[42] synthesized and characterized complexes of Copper (II) and Gold (I) with Clotrimazole and ketoconazole. It was found out that the ligands coordinated to Gold through imidazole N(1) atom of each ligand with linear structure. The clotrimazole and ketonazole coordinated to copper (II) through N (3) of the ligand atom with square planar structure. The new compounds were tested for *in vitro* activity against

cultures of *epimastigotes* of *trypanosoma cruzi*. At concentration equivalent to 10.6M of total clotrimazole and ketonazole in dimethylsulfoxide, all the complexes exhibited higher inhibitory activity than their respective parental compound.

Bankole *et al* reported the synthesis of organosilicon derivatives of p-aminosalicylic, salicylic and benzoic acids. It was discovered that the presence of silicon in the p-aminosalicyclic acid- silicon complex- prolonged and increased the antitubercular activity of p-amino salicyclic acid in the body.

Platinum complexes of 2–acetylpyriden thiosemi-carbazone have been synthesized in which intermolecular hydrogen bonds, π-π and weak pt– pt and pt– π contacts lead to aggregation and to a two– dimensional supra molecular assembly. The complexes were found to have a completely lethal effect on Gram +ve bacteria. Some of them showed effective antifungal activity towards yeast[43]. The effect of pt(II) and pd (II) complexes of 2–acetyl pyridine thiosemicarbazone (HACTSc) on sister chromatid exchange (SCE) rates, human lymphocyte proliferation kinetics and leukemia P388 have been investigated. Among these the compounds $[Pt(AcTsc)_2].H_2O$ and $[Pd(AcTsc)_2]$ were found to be the most effective in inducing antitumor and cytogenetic effect[44]. Antifungicidal, antibacterial and antifertility activities of biologically active hetrocyclic thiosemicarbzones and their coordination complexes with dimethylsilicone moiety have been described. Some ligands and their corresponding dimethylsilcon(IV) complexes have been tested for their effects on several pathogenic fungi and bacteria. The two representative complexes have been found to act as sterilizing agents by reducing the production of sperms in male mice[45].

Antihypertensive agents:

Essien and Coker, (1987)[46] reported the complexation of antihypertensive drug with calcium. Calcium nifedipine(Figure 9) was synthesized by reaction of calcium salt with nifedipine. The infrared spectrum revealed a strong evidence of possible complexation occurring at the carbonyl group (C=O) of the nifedipine. Two atoms of calcium complexed each to one pair of C=O groups of 2 molecules of nifedipine.

Recently, Golcu *et al*,(2005)[47] carried out the synthesis of binuclear copper (II) complex of Antihypertensive drug Pindolol. The biological activity of the parent drug pindolol was compared with the complex. The binuclear Cu(II) complex of pindolol was found to be highly active against *Bacillus megaterium, Aeromonas hydrophilia*, *Escherichia Coli*, *Candida albicans bacteries* and *Saccoramyces cerevisia*, *Rodotorula rubra, Kluyveromyces fragilis yeasts.* However, the free ligand was found not to be against these bacteria and yeasts.

In Analytical techniques:

Thiosemicarbazone have applications in anylitical fields also. Some of them produce highly colored complexes with metal ions. These complexes have been proposed as analytical reagents that can be used in selective and sensitive determination of metal ions[48-49]. Ferrocene derivatives containing thiosemicarbazone side chain have been investigated by cyclic voltametry and positron, annihilation life time (VPAL) measurements. Cu(II), Co (II) and Fe (II) in pharmaceutical propagation and solvent extraction with 2– acetylpyridine– 4– phenyl–3– thiosemicarbazone as complexing agent [50-51].

Thio and phenylthiosemicarbazones were applied as analytical reagents for the determination of various metal ions in different environmental samples (soil, water, human blood, *etc.*), food samples (leafy vegetables, medicinal leaves, *etc.*), pharmaceutical samples, synthetic mixtures and standard alloy samples. Based on this we conclude that the thio- and phenylthiosemicarbazones plays a vital role in the determination of metal ions at trace levels in real samples (environmental, pharmaceutical and medicinal leafy samples). Thio- and phenyl thiosemicarbazones are promising chelating agents for the analytical chemists working on the separation and determination of metal ions.

As Antibacterial agents:

Schiff base with metals such as thallium, molybdenum, manganese, zinc, cadmium, copper and silicon form complexes show impaired antimicrobial property when compared with Schiff base. Example- Schiff base of pyrolidone, pyridone with O-phenylenediamine and their metal complexes show better antibacterial activity.

Dimitra Kovala-Demertzi *et al.*[52] have been reported the antibacterial and antifungal activities of nickel(II) and palladium(II) complexes of 2-acetylpyridinethiosemi-carbazone. Antibacterial activities were evaluated against gram positive bacteria *Staphylococcus aureus* and gram negative bacteria *Escherichia coli*. Antifungal activity was evaluated against *Candida albicans*.

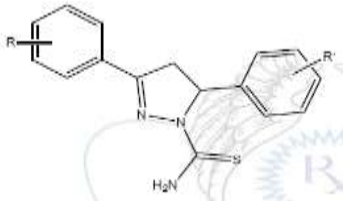
The antimicrobial activities of copper(II) and nickel(II) complexes with benzil *bis*thiosemicarbazone against the gram positive bacteria (*Bacillus macerans*) and gram negative bacteria (*Pseudomonas striata*) have been reported by Chandra *et al.*[53]. The authors reported that the metal chelates exhibit more inhibitory effects than

the parent ligand. Sathisha *et al.*[54] have reported the antibacterial and antifungal activities of the *bis*-isatinthiosemicarbazone complexes of copper(II), cobalt(II), nickel(II) and zinc(II) ions. The authors have evaluated the antibacterial activity against the bacteria *Bacillus cirroflagellosus* and antifungal activities against *Aspergillus niger* and *Candida albicans* by cup-plate method. The antibacterial activities of complexes of nickel(II), copper(II) and cobalt(II) with a series of thiosemicarbazone derivatives of 2-hydroxy-8-R-tricyclo-tridecane-13-one (R = H, CH3, C6H5) was reported by Rosu *et al.*[55]. Antibacterial activities are evaluated against five bacterial strains *i.e. Acinetobacter boumanii*, *Klebsiella pneumonia, Escherichia coli, Staphylococcus aureus* and *Pseudomonas auriginosa*.

Agarwal *et al.*[56] have reported the biological properties of copper(II) complex of 4[N-benzilidene) amino] antipyrinethiosemicarbazone (BAAPTS) and 4[N-(4'-methoxybenzilidene) amino]antipyrinethiosemicarbazone (MBAAPTS). The authors were evaluated the antibacterial activities of copper(II) complexes of BAAPTS, MBAAPTS and compared with the standard drugs (ampicillin and tetracycline) by agarcup method in dimethylformamide (DMF) solvent at a concentration of 50 µg mL-1. The antibacterial activities were evaluated against gram positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus* and gram negative bacteria, *Escherichia coli* and *Staphylococcus typhi*. Kuniaki *et al.*[57] have reported the synthesis of a tetrameric silver(I) cluster, [Ag(mtsc)4] from N-morpholyl-2-acetylpyridinethio-semicarabacarba-zone (mtsc) and silver(I) sources containing Ag-O bonds.
The authors have reported that the chloroform solution of tetrameric complex shows moderate activities against bacteria like *Bacillus subtilis*, *Staphylococcus aureus* and *Pseudomonas aeuruginosa* and effective activity against the yeast like *Candida albicans* and *Saccharomyces cerevisiae*. But it did not inhibit the growth of any selected microorganism in a watersuspension system. The lack of activity in water-suspension system can be attributed to the extraordinary stability or the low solubility of this complex. Noriko Chikaraishi Kasuga *et al.*[58] have reported the synthesis and antibacterial activity of twelve zinc(II) complexes of semi- and thiosemicarba-zones. Kizilcikli *et al.*[59] have reported antimicrobial activity of a series of thiosemicarbazones and S-alkylthiosemicarbazones. MIC values of the compounds were determined by the disc diffusion method against *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeurginosa, Salmonella typhi, Shigella flexneri, Staphylococcus aureus, Staphylococcus epidermidis* and *Candida albicans*. The thiosemicarbazones show antibacterial and antifungal effects with free ligand and metal complex forms. S-Alkylthiosemicarbazones did not affect the tested microorganisms but their zinc(II) complexes show selective activity.

As Antidepressant:

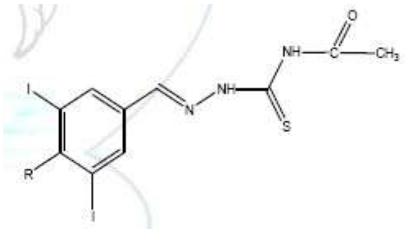
Chimenti F. *et al.* (2005),[60] synthesized a novel series of 1-thiocarbamoyl-3, 5-diaryl-4, and 5-dihydro--1 H--pyrazole derivatives and found to inhibit selectively A and B isoforms of monoamine oxidase (MAO). Most of compounds showed high activity against both the MAO-A and the MAO-B isoforms with *K*i values between 27 and 4 n M and between 50 and 1.5n M.



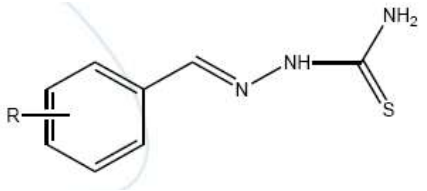
Structure of 1-thiocarbamoyl-3, 5-diaryl-4, 5-dihydro-(1*H*)-pyrazole derivatives

As Sedative & Hypnotics:

Rakhi Mishra *et al.* (2011)[61] synthesized a series of thiosemicarbazones by treating thiosemicarbazide with different substituted aromatic aldehydes and then these compounds were further treated with acetic anhydrides to obtain acylated compounds respectively. The synthesized compounds were tested for locomotor activity by actophotometer apparatus. Healthy male albino mice of approximately same age, weighing about 25-30 gm were used and were divided in to 3 groups. They were maintained under standard conditions (12 hr light/ 12 hr dark cycle, 25 ± 30C, 36-60 % humidity). One group served as positive control (received chlorpromazine 3mg/kg; i.p), one group as negative control (received 5% gum acacia 5 ml/kg) and rest of the groups received test compounds (80 mg/kg orally. The sedative hypnotic activity of mice was observed by recording actophotometer readings after every 30 mins for 120 mins. In actphotometer method amongst the entire tested compounds acylated compound showed better activity than thiosemicarbazones, a few showed activities even better than standard



Structure of Thiosemicarbazones derivatives



Structure of Substituted benzaldehydethio-semicabazone derivatives

Miscellaneous application:

The complexes of dithiocarbamate ligands like dithiocarbomate themselves have practical application in agriculture and for treatment of alcoholisim.[62-63]

Mixed ligand complexes play an important role in numerous chemical and biological systems like water softening, ion exchange resins, electroplanting, dying, antioxidant, photosynthesis, excretion of undesirable and harmful metal from living organisms. Many of these complexes shown good biological acitivity against pathogenic micro – organism[64-68]. Mixed ligands complexes are suitable for mimicking the role of metal ions detoxification mechanism and drug designing. Termay complexes containing an amino acid as secondary ligands are of significance as potential models for enzymes metal ion substrate complexes.

Schiff base metal complexes possess significant antifertility and enzymatic activity[69]. Also chromium azomethine complexes, cobalt complex of Schiff bases are used in dyes for giving color to leathers, food package and wool[70].

CONCLUSION:

Schiff' bases and their transition metal complexes possess a number of biological applications. Metal complexes show higher activity than free ligands. These compounds shows bright path towards pharmaceutical as well as chemical sciences. But still there is need to explore the biological properties of these already synthesized metal complexes with Schiff bases and to synthesize new complexes with more properties.

The Chemistry of Schiff bases is a field that is being noticed. Schiff base ligands are considered privileged ligands because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines.

From the survey we reveal that thio- and phenylthiosemicarbazones are good chromogenic reagents for the separation and determination of metal ions due to strong chelating ability of the hydrazine nitrogen (C=N) and thioketonic (C=S) group. The present survey concludes that the thio and phenylthiosemicarbazones were employed for the separation and determination of the metal ions such as Cu(II), Pd(II), Co(II), Ni(II), Zn(II), Cd(II), Mo(VI), Fe(III), Pb(II), V(V), V(IV), Ru(III), Pt(IV), Ag(I), Ga(III), Tl(III), Cr(VI), Hg(I), Cu(I),Hg(II), Au(III) and Mn(II) from various sources.

Thiosemicarbazones are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, and as raw material for drug synthesis. The advances in the use of Thiosemicarbazone for organic synthesis during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported in this review and in the accompanying supplementary information. The survey of the literature revealed that, Thiosemicarbazone is a versatile lead molecule for designing potential bioactive agents, and its derivatives were reported to possess broad-spectrum anticonvulsant, anxiety activities and other biological activity. Further we can conclude that many other derivatives of Thiosemicarbazone can be synthesized which will be expected to show potent pharmacological activities.

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